

Achieving large coefficient of variation in subthalamic neurons exhibiting type-1 phase response curve behavior

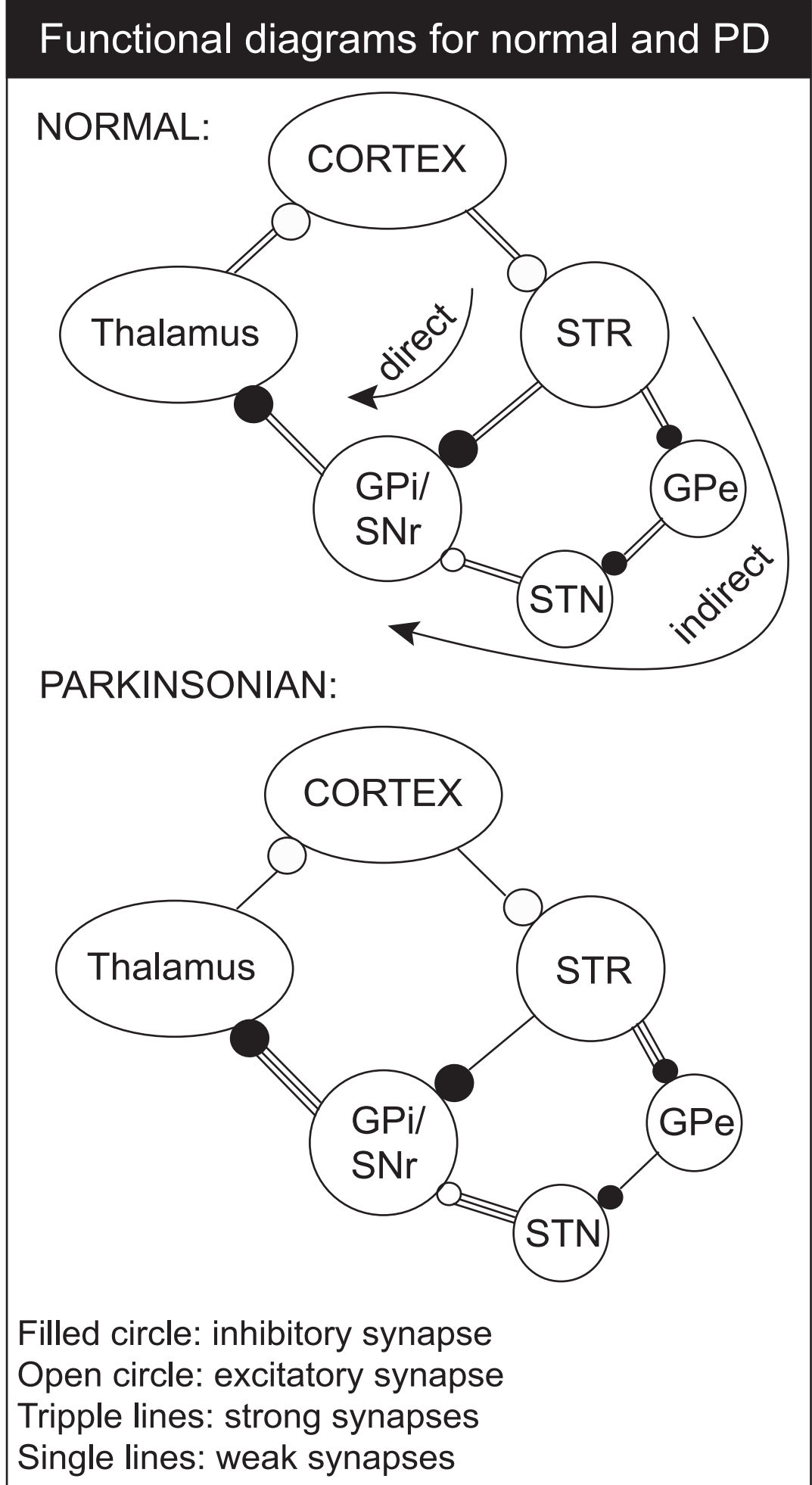
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Motivation:

Subthalamic nucleus (STN) plays crucial role in indirect pathway and contributes to sustained self-oscillatory mechanism, while displaying high coefficient of variation



(CV) of interspike intervals at high frequencies in *in vivo*.

STN firing patterns
[C. J. Wilson, M. D. Bevan, 2011]

In vivo:

Firing rates: 7-12 Hz, 18-28 Hz
regular, irregular (most common), bursty.

In vitro:

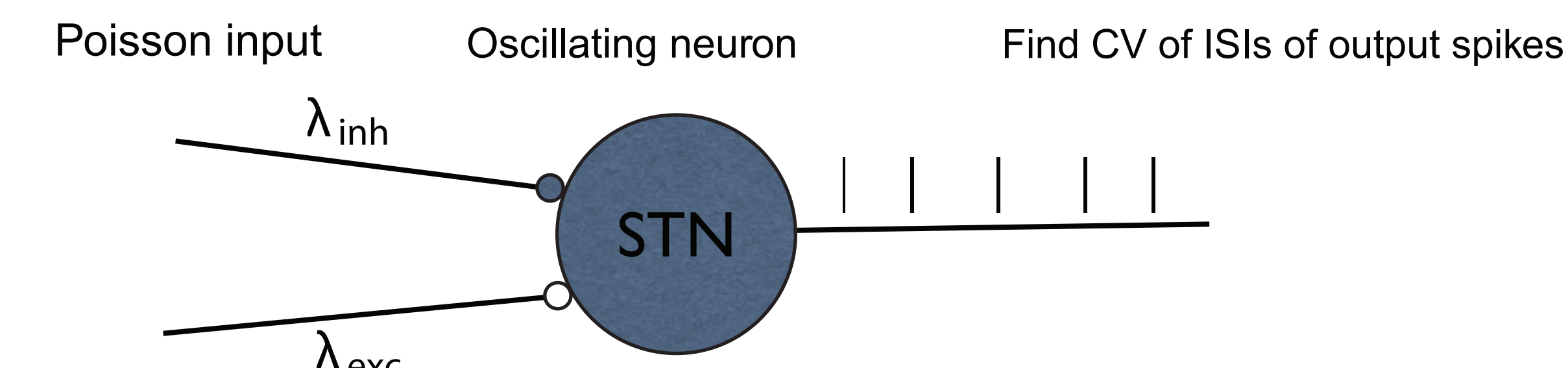
Firing rates: 7-12 Hz
regular (most common)
bursty

CV of ISIs (intact rats):
0.8 (non-bursty, 37%)
to 1.3 (bursty, 63%)
[D. S. Kreiss, et al. 1997]

The main goal of our work is to understand mechanisms, using modeling, of STN neurons in exhibiting high firing rates while also displaying high CVs at the same time.

Methods:

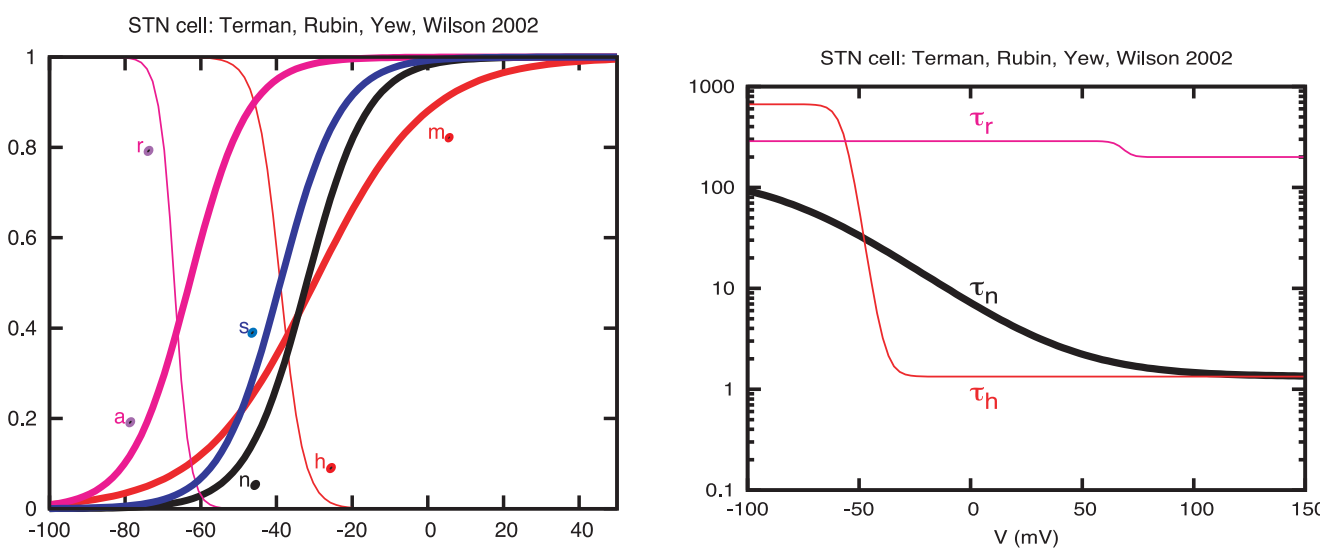
We idealize the situation by considering a single-compartment model with inhibitory as well as excitatory (for example from Cortex) synaptic inputs.



We use the well known Terman et al. 2002 model (*J. Neurosci.* 22:2963-2976) that also incorporates low-threshold calcium current, and Wang and Buzsaki 1996 model (*J. Neurosci.*

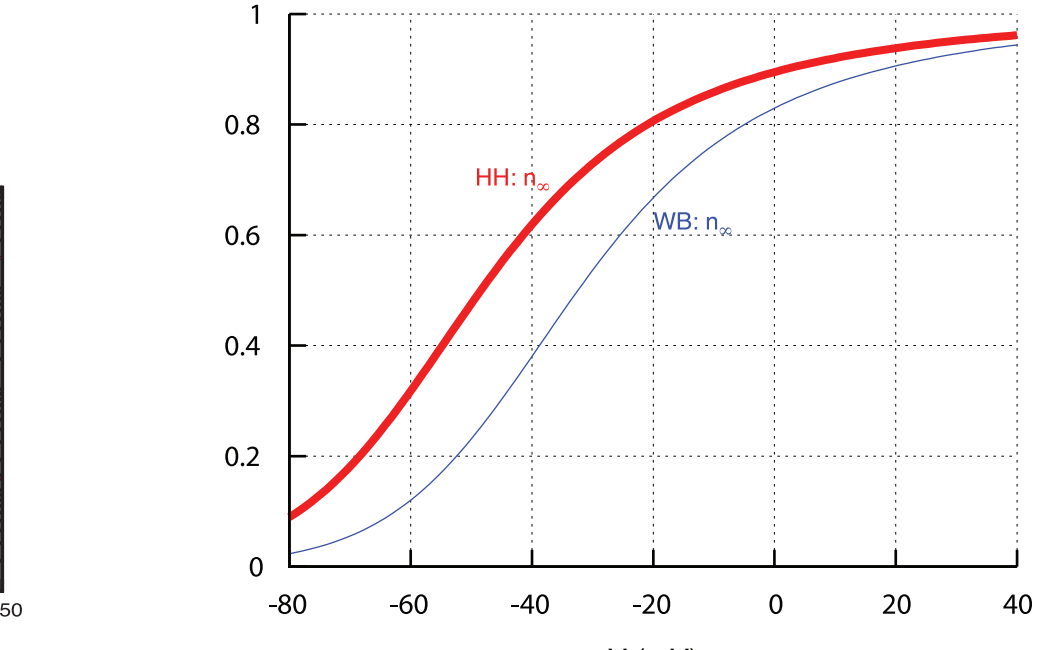
Terman et al. 2002 model:

Na^+ , K^+ , Ca^{2+} , T, AHP, Leakage



Wang and Buzsaki 1997 model:

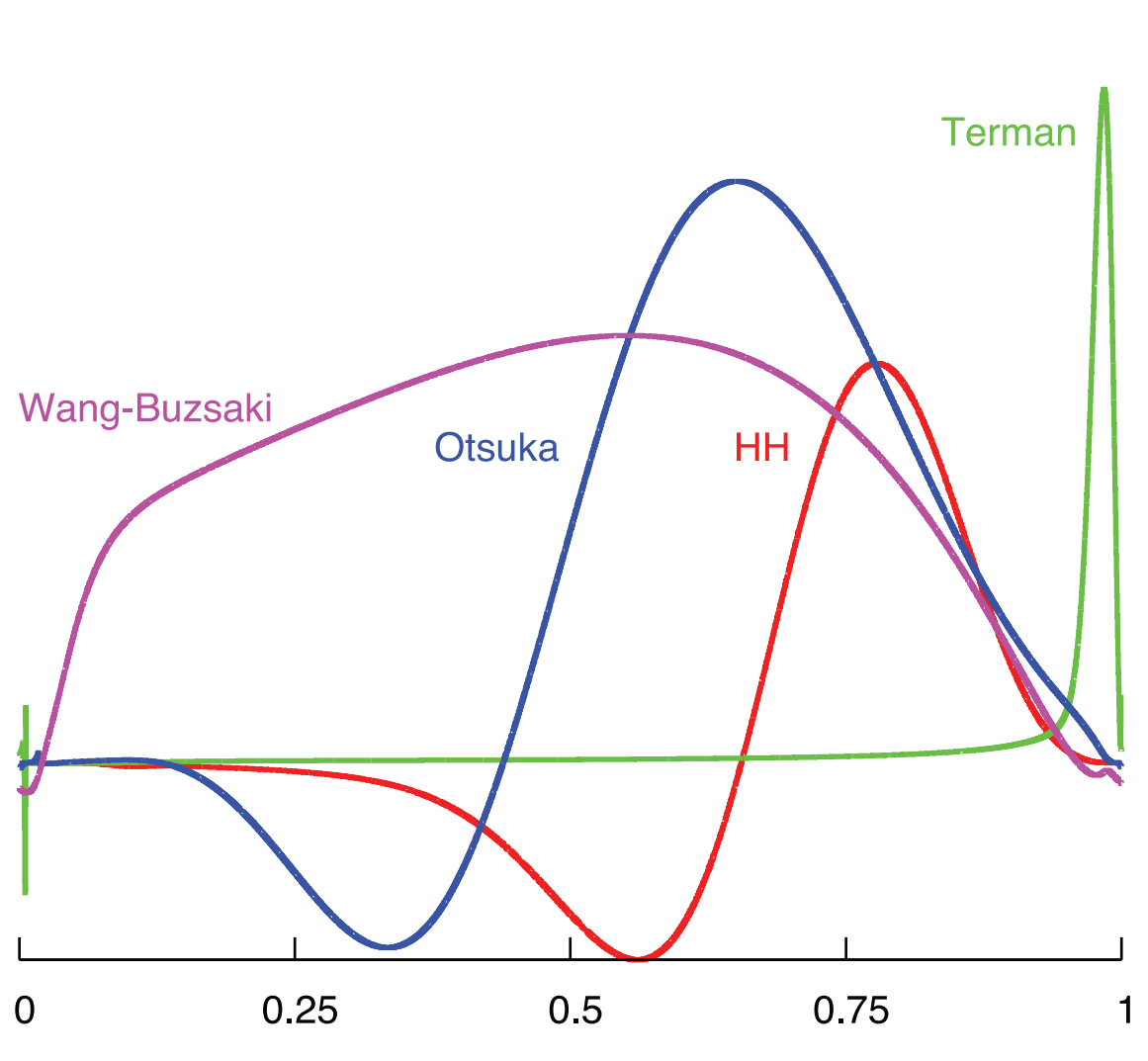
Na^+ , K^+



$$\frac{d[\text{Ca}]_{\text{in}}}{dt} = \epsilon(-I_{\text{Ca}} - I_T - k_{\text{Ca}}[\text{Ca}]_{\text{in}})$$

$$I_T = G_T a_{\infty}^3 b_{\infty}^2 (V - E_{\text{Ca}})$$

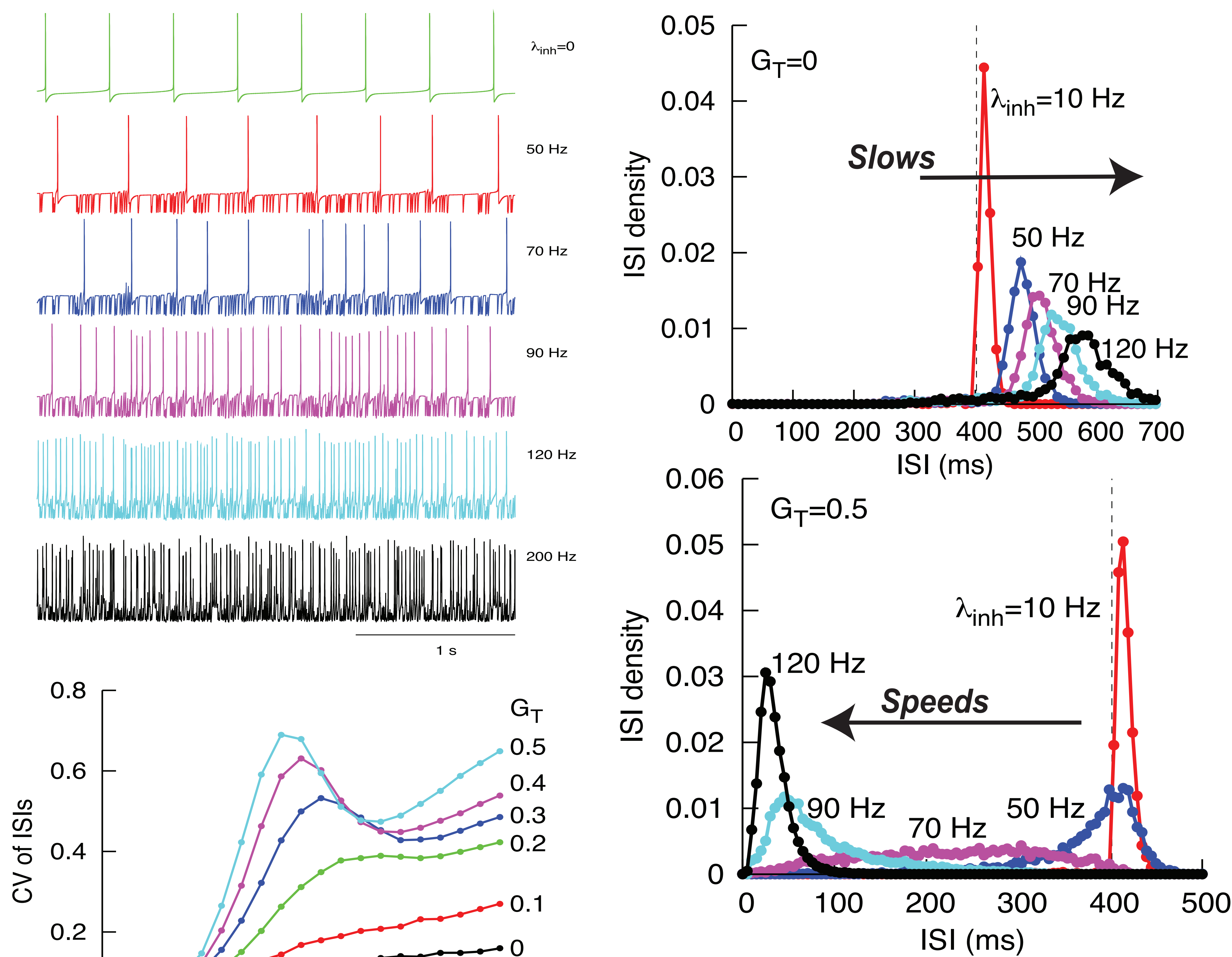
$$b_{\infty} = \frac{1}{1 + e^{(r - \theta_b)/\sigma_b}} - \frac{1}{1 + e^{-\theta_b/\sigma_b}}$$



Terman et al.'s and Wang and Buzsaki's models both display type-1 PRCs, and thus in effect respond with similar (but not identical) spike time variations to input stimuli.

Achieving high CV using fast inhibition:

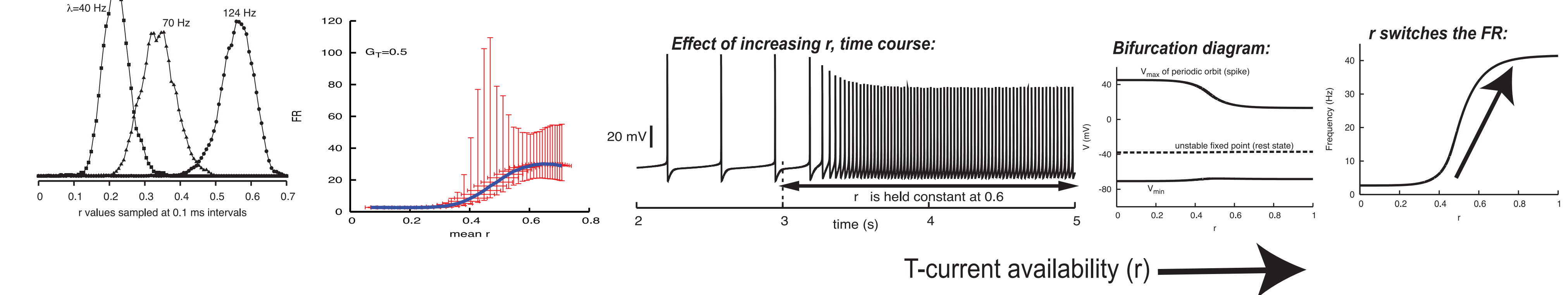
Here we use Terman et al.'s model to demonstrate how fast inhibitory synaptic input can result in high CVs and firing rates. If T-current is turned off, then the neuron slows down with only moderate increase in its CV. The activation of the T-current facilitated faster rate and higher CV.



The coefficient of variation (CV) is shown for different levels of the maximal conductance of the T-current (G_T) as a function of inhibitory synaptic drive frequency.

Mechanism using fast inhibition:

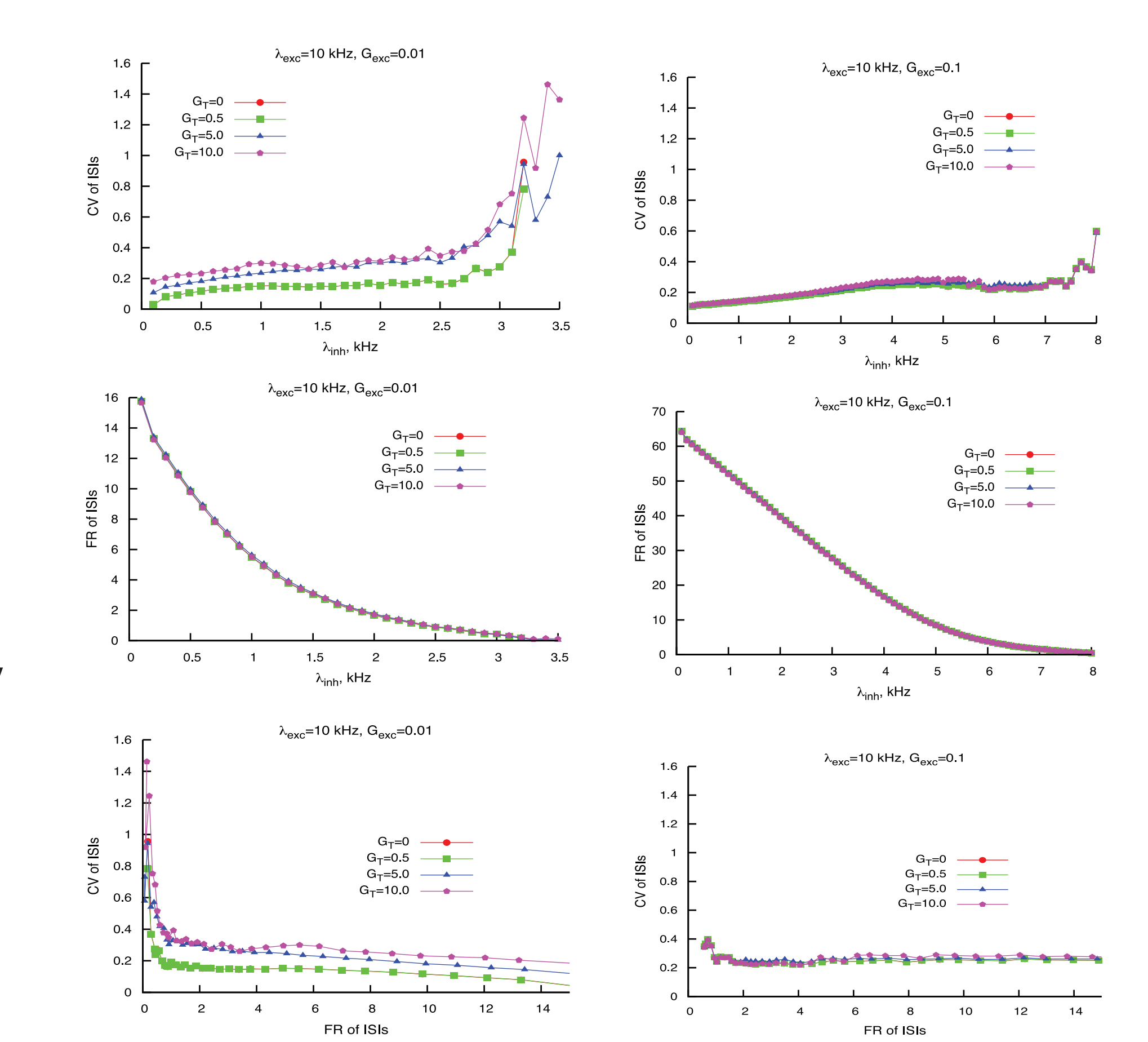
T-current availability (r) increases at high input rates
T-current availability as a parameter



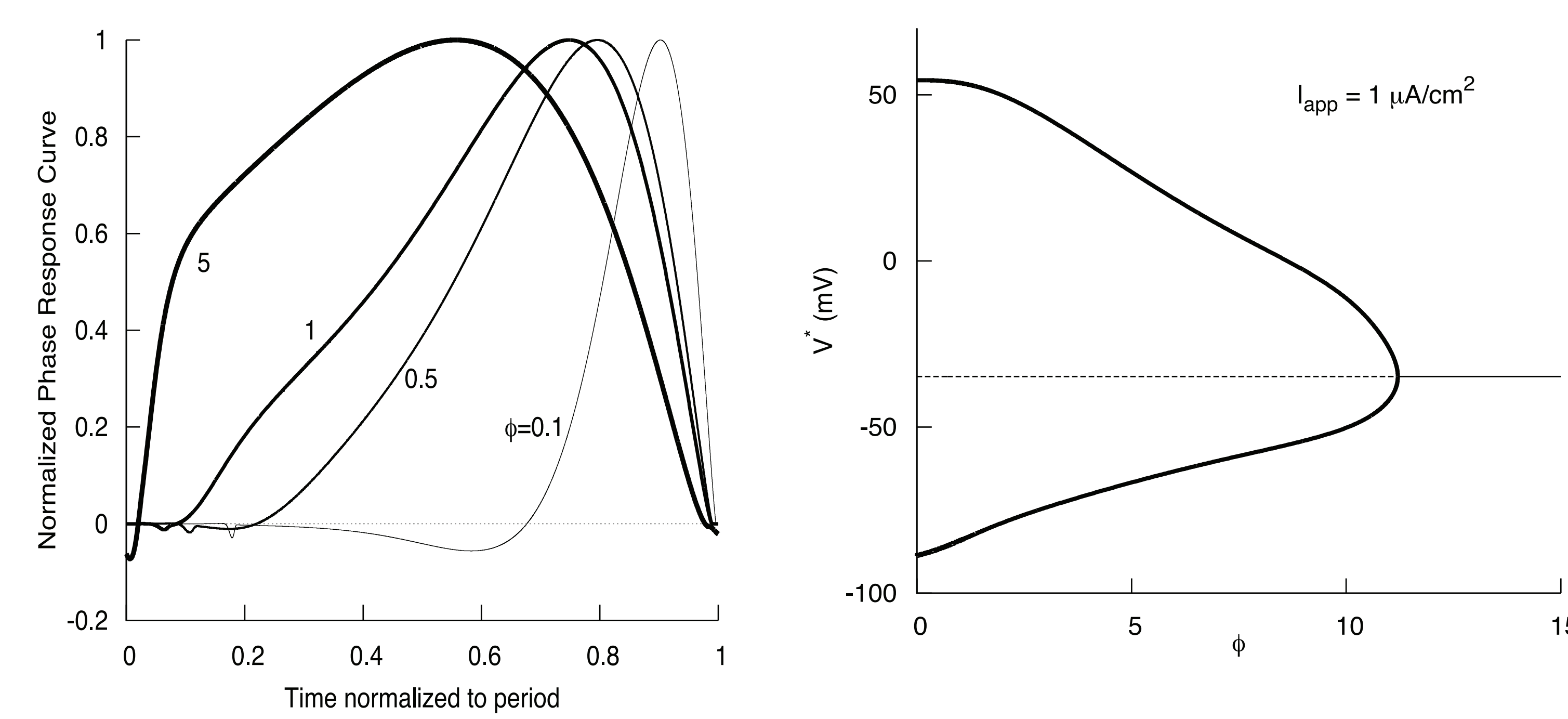
Effect of slow inhibition:

If slow synaptic time constants (10 ms, right figures) are used, CV hovers around 0.3 for most input rates. It is only at very small firing rates that the CV can be enhanced significantly.

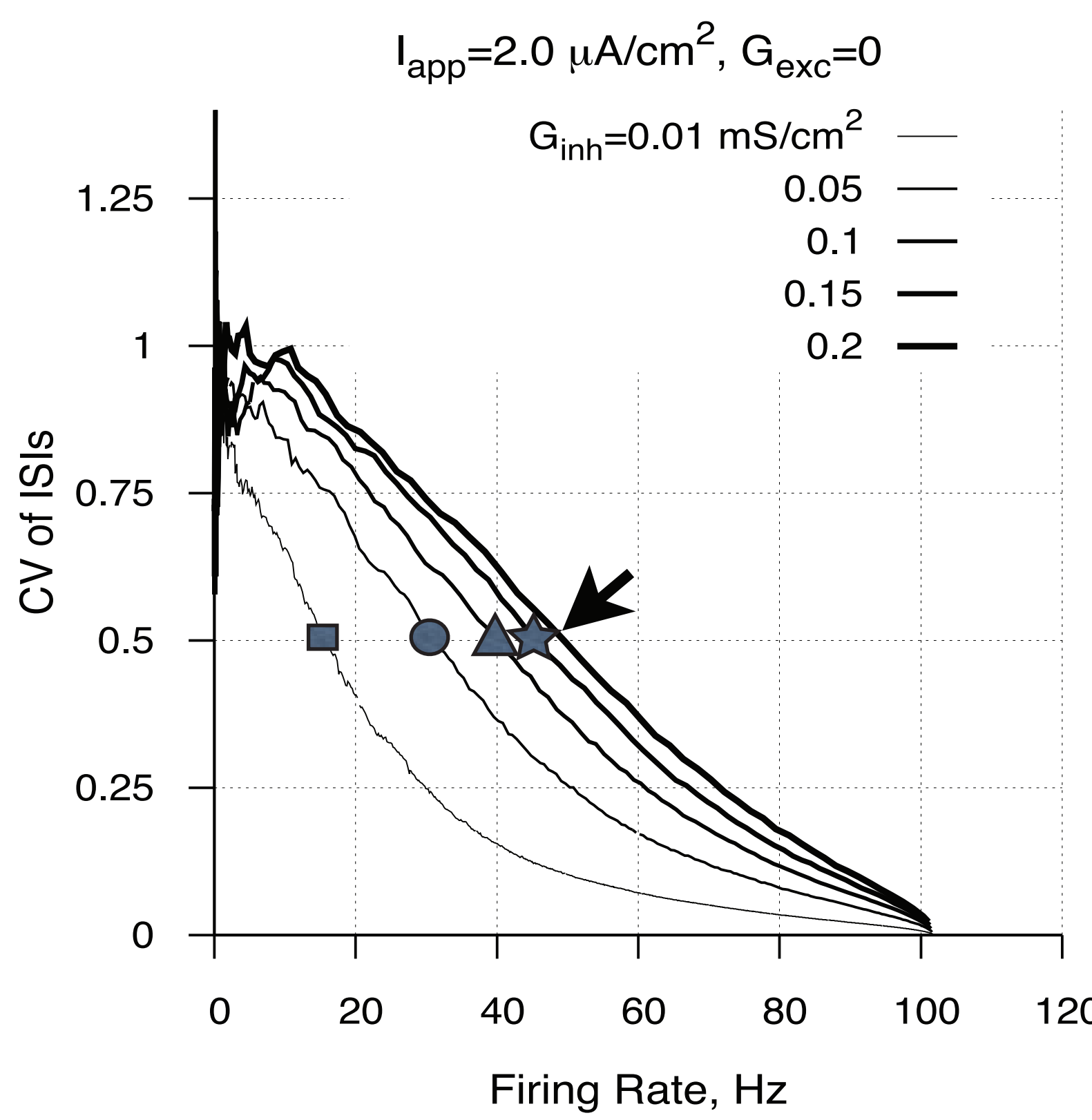
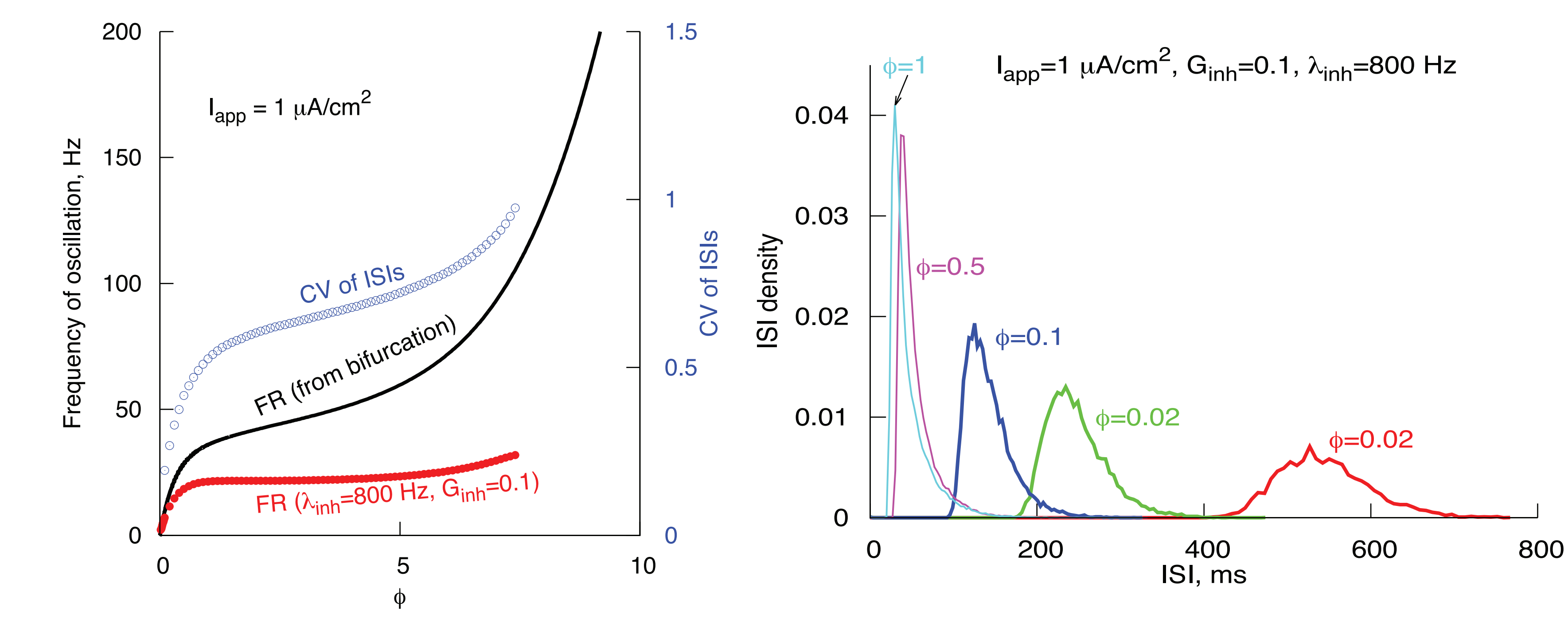
Firing rates can be elevated by the presence of random synaptic excitatory input, but the CV still remains small. In fact when the excitatory input is large, the membrane is depolarized far above the T-current activation window leading to lessening of the T-current effect.



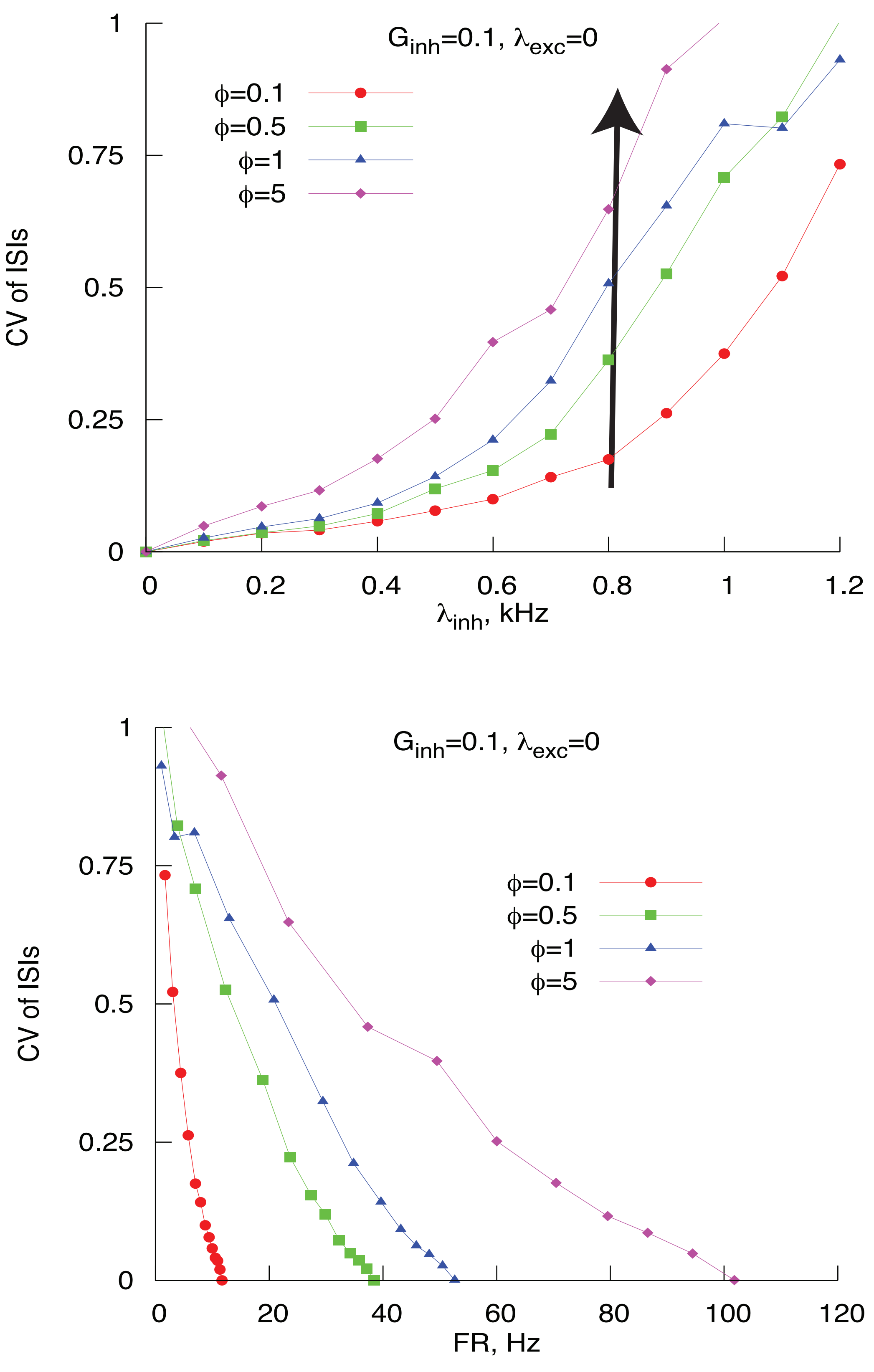
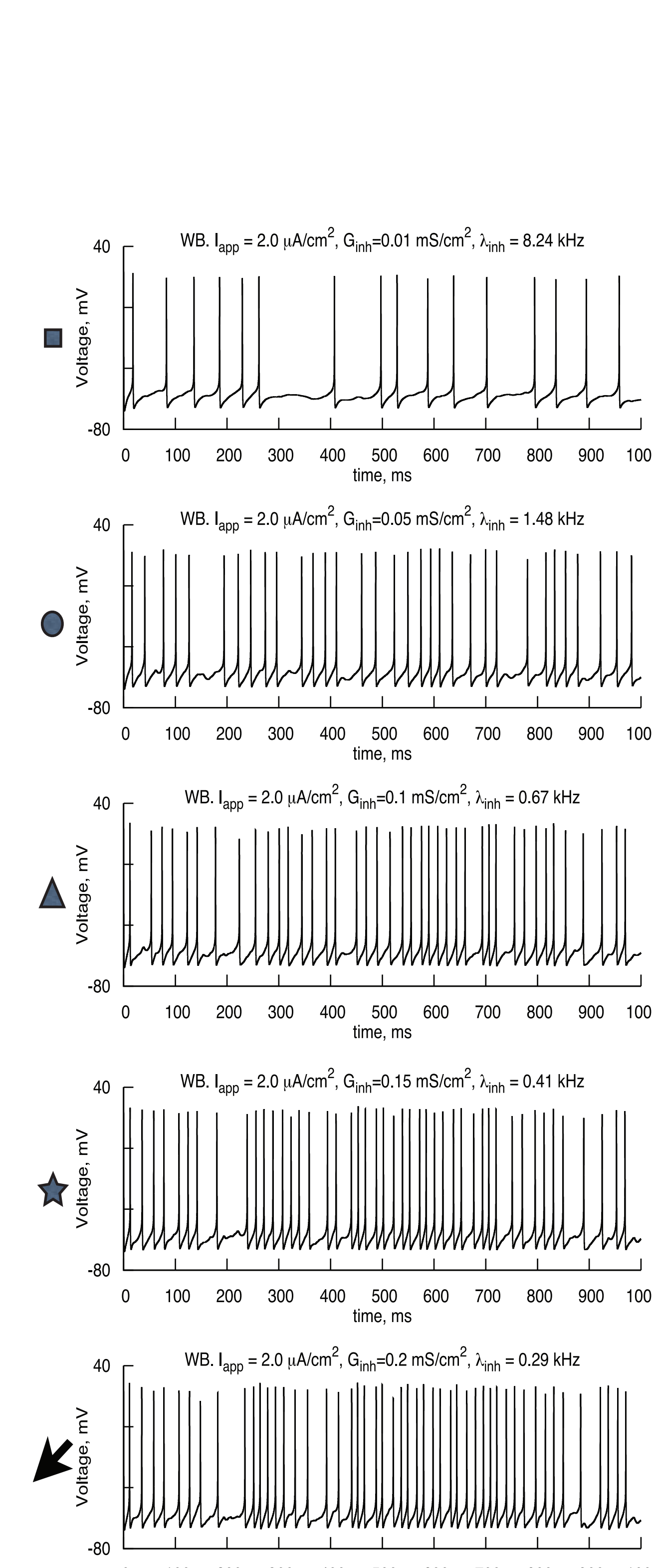
Achieving high CV by altering phase sensitivity:



Here we use Wang and Buzsaki model, and alter phi that alters the time constants of sodium inactivation and potassium activation. Inhibitory synaptic input timed at Poisson intervals of different rates is applied. Strong input and large phi both result in high CV. Increasing phi increases the phase sensitivity at small input phases and consequently increases the intrinsic oscillation frequency. When inhibitory synaptic input is present, the ISI distribution acquires finite width and long tail. Maximum growth in the CV as a function of phi occurs when the growth of the firing rate itself is maximum.



The parameter phi is capable of altering the shape and in particular the skewness of the PRC, and thus being able to alter the sensitivity of the model to inputs at various phases. Higher sensitivity imparted by bigger values of phi could cause larger spike time deviations resulting in higher CV.



A third mechanism to enhance the coefficient of variation is to utilize the network properties of the STN and GPe connectivity. T-current dynamics with less phase sensitivity as in Terman et al.'s model may also help increase the CV of the STN neurons.

Conclusions:

Subthalamic neurons require no external input in order for them to exhibit sustained spiking behavior. Such behavior is markedly different from neurons that would fire in response to cumulative synaptic inputs. Thus the observations in *in vivo* experiments of these neurons exhibiting high levels of coefficient of variation (CV) among their interspike intervals is difficult to explain. We propose two mechanisms under which subthalamic neurons and other such neurons that exhibit type-1 phase response curves could display high levels of coefficient of variation among their interspike intervals.

1. Fast inhibitory synaptic input: Low threshold calcium currents can get activated in response to fast inhibition, elevating their CV while at the same time increasing their firing rate.
2. If internal currents could alter the phase sensitivity of the underlying neuron, then a higher CV can be achieved. Higher firing rates can be achieved by using excitatory input.

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